Exhibit a

# Goodman and Gilman's The Pharmacological Basis of Therapeutics

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above, the enzymes of crucial metabolic or regulatory pathways (*e.g.*, dihydrofolate reductase, acetylcholinesterase), proteins involved in transport processes (*e.g.*, $Na^+,K^+$-ATPase), or proteins that serve structural roles (*e.g.*, tubulin). Specific binding properties of other cellular constituents can also be exploited. Thus, nucleic acids are important drug receptors, particularly for chemotherapeutic approaches to the control of malignancy.

The binding of drugs to receptors can involve all known types of interactions—ionic, hydrogen, hydrophobic, van der Waals, and covalent. In most interactions between drugs and receptors it is likely that bonds of multiple types are important. If binding is covalent, the duration of drug action is frequently, but not necessarily, prolonged. Noncovalent interactions of high affinity may also appear to be essentially irreversible.

**Structure–Activity Relationship.** Both the affinity of a drug for its receptor and its intrinsic activity are intimately related to its chemical structure. The relationship is frequently quite stringent. Relatively minor modifications in the drug molecule, including such subtle changes as stereoisomerism, may result in major changes in pharmacological properties. Exploitation of structure–activity relationships has on many occasions led to the synthesis of valuable therapeutic agents. Because changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to toxic effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug. Therapeutically useful antagonists of hormones or neurotransmitters have been developed by chemical modification of the structure of the physiological agonist. Minor modifications of structure can also have profound effects on the pharmacokinetic properties of drugs.

Given adequate information about both the molecular structures and the pharmacological activities of a relatively large group of congeners, it should be possible to identify those properties that are required for optimal action at the receptor—size, shape, the position and orientation of charged groups or hydrogen bond donors, and so on. Although this goal is rarely approached in practice, recent advances in computational chemistry and structural analysis of organic compounds have given new impetus to the quantitation of structure–activity relationships and drug design. Molecular modeling of drug binding sites has been used to predict the placement of functional groups in the drug molecule to enhance activity or selectivity or to alter pharmacokinetic properties. This practice is a sharp departure from the traditional quasi-random synthesis and screening of congeners. More exciting are recent advances in using the structures of receptors, determined at atomic resolution by X-ray crystallography, for the initial design of ligands. To date, this approach has been restricted to soluble drug receptors, generally enzymes. However, the ability to clone and express DNA molecules that encode less abundant regulatory proteins and increasing success in the crystallization of membrane-bound proteins hold great promise for drug design based on a detailed knowledge of the drug binding site and the effect of drug binding on receptor structure (*see* Marshall, 1987).

**Cellular Sites of Drug Action.** The sites at which a drug acts and the extent of its action are determined by the localization and functional capacity of the specific receptors with which the drug interacts and the concentration of drug to which the receptor is exposed. Selective localization of drug action is therefore not necessarily dependent upon selective distribution of the drug. If a drug acts on a receptor that serves functions common to most cells, its effects will be widespread. If the function is a vital one, the drug will be particularly difficult or dangerous to use. Nevertheless, such a drug may be clinically important. Digitalis glycosides, important in the treatment of heart failure, are potent inhibitors of an ion transport process that is vital to most cells. As such, they can cause widespread toxicity, and their margin of safety is dangerously low. Other examples could be cited, particularly in the area of cancer chemotherapy.

If a drug interacts with receptors that are unique to only a few types of differentiated cells, its effects are more specific. The hypothetical ideal drug would cause its therapeutic effect by virtue of such types of action. Side effects would be minimized, but toxicity might not be. If the differentiated function were a vital one, this type of